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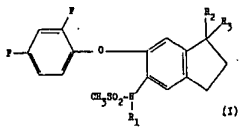
(54) **Novel Indianyl Derivatives**

(57) Novel indanyl, derivatives of the general formula I



(I)

(in which R_1 represents H, methanesulphonyl or acetyl and R_2 and R_3 together represent oxo or oximino or R_2 represents H and R_3 represents H, hydroxyl or amino) and physiologically tolerable salts with acids of such compounds in which R_2 is H and R_3 is amino have *inter alia* an anti-inflammatory activity and accordingly may be made up with suitable carriers into pharmaceutical preparations.

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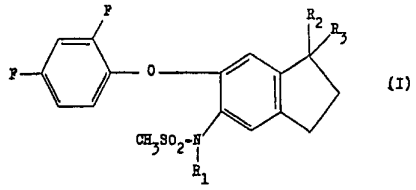
SPECIFICATION

Novel Indanyl Derivatives and their Manufacture and Use

The present invention is concerned with novel indanyl derivatives and with their manufacture and use.

The present invention provides indanyl derivatives of the general formula I



(I)

in which

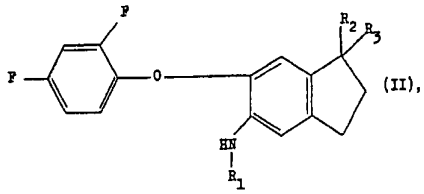
R_1 represents a hydrogen atom, a methanesulphonyl group or an acetyl group, and

R_2 and R_3 together represent an oxo group or an oximino group or R_2 represents a hydrogen atom and R_3 represents a hydrogen atom, a hydroxyl group or an amino group, and

physiologically tolerable salts with acids, for example hydrochlorides, of such compounds in which R_2 represents a hydrogen atom and R_3 represents an amino group.

The new compounds of the present invention may be prepared by the process of the present invention, as defined below.

The present invention also provides a process for the manufacture of a compound of the general formula I or a physiologically tolerable salt with an acid of such a compound in which R_2 represents a hydrogen atom and R_3 represents an amino group, wherein a compound of the general formula II



(II),

in which R_1, R_2 and R_3 have the meanings given above, is condensed with methanesulphonyl chloride, and, if desired, in any resulting compound of the general formula I in which R_2 and R_3 together represent an oxo group this oxo group is converted into an oximino group, and/or in any resulting compound of the general formula I in which R_2 and R_3 together represent an oxo or oximino group this oxo or oximino group is reduced to form a compound of the general formula I in which R_2 represents a hydrogen atom and R_3 represents a hydroxyl or amino group, respectively, and/or any resulting compound in which R_1 represents a hydrogen atom is acetylated, and/or any resulting salt is converted into the corresponding free compound, and/or any resulting compound of the general formula I in which R_2 represents a hydrogen atom and R_3 represents an amino group is converted into a physiologically tolerable salt thereof with an acid.

The process of the present invention for the manufacture of the novel indanyl derivatives may be carried out in a manner known *per se*, for example under the conditions described in European Patent Application No. 0 009 554. In comparison with the indanyl derivatives described in that Application (with the exception of compounds of the general formula I in which R_2 and R_3 represent an oximino group, which are preferably used as intermediates), the compounds of the present invention are distinguished by a superior anti-inflammatory activity, as the results of the adjuvant-arthritis test described as follows show:

Male and female rats of the strain Lewis (LEW) in a weight range of between 110 and 190 g were used. The animals received drinking water and Altromin compressed feed *ad libitum*.

10 rats were used for each dosage group.

Mycobacterium butyricum obtained from the firm Difko, Detroit, was used as irritant. A suspension of 0.5 mg of *Mycobacterium butyricum* in 0.1 ml of thinly liquid paraffin (DAB 7) was injected subplantar into the right hindpaw.

Starting from the 11th day of the test, the test substances were given orally daily over a period of 4 days. The substances were administered in the form of a clear solution or in the form of a crystalline suspension with the addition of Myrj 53 (85 mg %) in an isotonic sodium chloride solution.

The rats were divided as uniformly as possible into different groups with regard to their body weight. After measuring the volume of the right handpaw by plethysmography, 0.1 ml of adjuvant was injected subplantar into the paw.

The right hindpaw was measured from the 14th day of the test to the end of the test. The duration of the test was three weeks.

The healing of the right hindpaw of the animal as a function dependent on the dose of test substance administered was determined.

The following Table lists the results obtained in this test for compounds 3 to 5 of the present invention in comparison with indanyl derivatives 1 and 2 known from European Patent Application No. 0 009 554, which are of analogous structure. The results show that the compounds of the present invention have a good action at low dosages, whereas the substances used for comparison exhibited practically no activity at such low dosages.

No.	*Substance*	*Substance mg/kg animal*	*% Healing of the right hindpaw*
1	N-[6-(4-Fluorophenoxy)-5-indanyl]-methanesulphonamide	4x0.1 4x0.3	0 0
2	N-[6-(2,4-Dichlorophenoxy)-5-indanyl]-methanesulphonamide	4x0.1 4x0.3	0 3
3	N-[6-(2,4-Difluorophenoxy)-5-indanyl]-methanesulphonamide	4x0.1 4x0.3	33 40
4	N-Acetyl-N-[6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide	4x0.1 4x0.3	28 38
5	6-(2,4-Difluorophenoxy)-5-methylsulphonyl-amino-1-indanone	4x0.1 4x0.3	36 42

The novel compounds of the present invention are thus suitable, in combination with the carriers that are customarily used in, for example, galenical pharmacy, for the treatment of *inter alia* diseases of the rheumatic type (for example osteoarthritis or ankylosing spondylitis), bronchial asthma and hay fever.

It is also remarkable that the novel indanyl derivatives of the general formula I and the aforesaid physiologically tolerable salts are suitable also for the treatment of migraine and of dysmenorrhoea, and reduce the risk of thrombosis.

Surprisingly, among the novel compounds of the present invention there are also to be found those which in addition to an anti-inflammatory activity also exhibit a pronounced anti-ulcerogenic as well as a tumour-inhibiting activity.

The present invention accordingly further provides a compound selected from compounds of the general formula I and physiologically tolerable salts with acids of such compounds in which R_2 represents a hydrogen atom and R_3 represents an amino group, for use in a method of treatment by therapy of an inflammation.

The present invention further provides a pharmaceutical preparation which comprises a compound selected from compounds of the general formula I and physiologically tolerable salts with acids of such compounds in which R_2 represents a hydrogen atom and R_3 represents an amino group, in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may contain one or two of the active compounds of the present invention.

The pharmaceutical preparation may be in a form suitable, for example, for oral administration.

The pharmaceutical preparations may be manufactured in the customary manner by converting the active substances, together with suitable additives, carriers and flavour-correctants, into the desired forms of administrations, for example tablets, dragées, capsules, solution and inhalants.

Especially suitable for oral use are tablets, dragées and capsules that contain, for example, from 1 to 250 mg of active substance and from 50 mg to 2 g of pharmacologically inactive carrier, for example lactose, amylose, talcum, gelatine, magnesium stearate and the like, as well as the usual additives.

The following Examples illustrate the invention:

Example 1

a) 10.1 g of 5-bromo-6-nitroindane, 4.1 g of copper(I) chloride, 7.1 g of potassium tert.-butanolate and 8.5 g of 2,4-difluorophenol were boiled in 210 ml of tert.-butanol for 7 hours. Cooling, dilution with ether, filtration, concentration, taking up of the residue in ether, washing the ethereal

solution with 1N hydrochloric acid as well as drying and concentration yielded 10.5 g of the crude product which was chromatographed over a silica gel column with hexane/ethyl acetate. Yield: 6.3 g of 5-(2,4-difluorophenoxy)-6-nitroindane having a melting point of from 65 to 68°C (from hexane).

b) 10 g of Raney nickel were added to 14.6 g of 5-(2,4-difluorophenoxy)-6-nitroindane in 300 ml of dioxan/ether 1:1 and then, at 40°C, 4.86 ml of hydrazine hydrate were added thereto. After a further 30 minutes at 50°C and 30 minutes under reflux the whole was cooled, filtered and concentrated. Yield: 13 g of crude 6-(2,4-difluorophenoxy)-5-indanylamine.

c) 4.0 ml of methanesulphonyl chloride were added at 0°C to 13.1 g of 6-(2,4-difluorophenoxy)-5-indanylamine in 60 ml of pyridine. After 3 hours at 0°C and 16 hours at 20°C, the whole was concentrated and the residue was taken up in chloroform; the resulting solution was washed with 1N hydrochloric acid and concentrated. Recrystallization of the residue from ethanol yielded 8.1 g of N-[6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide having a melting point of from 85 to 87°C.

Example 2

Under a nitrogen atmosphere and at 0°C, 1.5 ml of acetic anhydride were added within a period of 10 minutes to 3 g of N-[6-(2-difluorophenoxy)-5-indanyl]-methanesulphonamide in 30 ml of pyridine and the whole was then stirred for 3 hours at 0°C and for 13 hours at room temperature. Concentration was then carried out, and the residue was taken up in chloroform and extracted by shaking three times with 1N hydrochloric acid and once with water; the organic phase was dried over calcium sulphate and concentrated and the residue was recrystallized from ethanol. Yield: 3.1 g of N-acetyl-N-[6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide having a melting point of 160°C.

Example 3

8.3 ml of methanesulphonyl chloride were added at 0°C to 12.8 g of 5-amino-6-(2,4-difluorophenoxy)-1-indanone in 95 ml of pyridine. After 3 hours at 0°C and 16 hours at 20°C, the whole was concentrated, the residue was taken up in chloroform and the resulting solution was washed with 1N hydrochloric acid and concentrated. Chromatography of the residue over silica gel with dichloromethane/ethyl acetate yielded 1.2 g of 6-(2,4-difluorophenoxy)-5-bis-(methylsulphonyl)-amino-1-indanone having a melting point of 190°C (from toluene), followed by 8.9 g of 6-(2,4-difluorophenoxy)-5-methylsulphonylamino-1-indanone having a melting point of 153°C (from ethanol).

The indanone starting material for this synthesis step may be obtained by either of the following two methods:

Method 1

a) 40 ml of acetic anhydride were added at 30°C to 13.9 g of 6-(2,4-difluorophenoxy)-5-indanylamine in 93 ml of acetic acid. A solution of 11 g of chromium trioxide in 27 ml of water and 17 ml of acetic acid was then added dropwise at 50°C. After a further 40 minutes at 50°C, the whole was cooled, poured onto ice water and filtered with suction. The residue was chromatographed over silica gel with dichloromethane/ethyl acetate. There were thus obtained 9 g of 5-acetylamino-6-(2,4-difluorophenoxy)-1-indanone having a melting point of 153°C, followed by 4 g of the isomeric 6-acetylamino-5-(2,4-difluorophenoxy)-1-indanone having a melting point of 199°C.

b) 12.9 g of 5-acetylamino-6-(2,4-difluorophenoxy)-1-indanone were boiled in 210 ml of ethanol with 22 ml of concentrated hydrochloric acid for 2 hours. The whole was then concentrated, water and an ammonia solution were added to the residue (pH 8) and the solid, 5-amino-6-(2,4-difluorophenoxy)-1-indanone, was filtered off with suction. Yield: 11.1 g having a melting point of 132°C.

Method 2

a) 4.58 g of 5-(2,4-difluorophenoxy)-6-nitroindane and 8.2 g of bis-(dimethylamino)-tert.-butoxy-methane were stirred in 5 ml of dimethylformamide at 140°C for 60 minutes. Concentration *in vacuo* yielded crude 1-dimethylaminomethylene-5-(2,4-difluorophenoxy)-6-nitroindane.

b) This product was dissolved in chloroform and, at −40°C, ozone was introduced (for 12 minutes at a rate of 4.5 g per hour). After the introduction of nitrogen, the whole was poured onto ice water, adjusted to pH 3 with hydrochloric acid, washed with a sodium bisulphite solution and concentrated. Chromatography of the residue over silica gel with chloroform yielded 250 mg of 5-(2,4-difluorophenoxy)-6-nitro-1-indanone having a melting point of 145°C (from ethanol).

c) This product was dissolved in 5 ml of ethanol/dioxan 1:1, 250 mg of Raney nickel were added and then, at 45°C, 100 mg of hydrazine hydrate were added. After 30 minutes under reflux, the whole was cooled, filtered and concentrated. Yield: 240 mg of 5-amino-6-(2,4-difluorophenoxy)-1-indanone having a melting point of 135°C (from ethanol).

Example 4

1.57 g of acetyl chloride were added to 2.82 of 6-(2,4-difluorophenoxy)-5-methylsulphonylamino-1-indanone in 30 ml of pyridine. After 20 hours at 20°C, concentration was carried out, water was added, and the whole was adjusted to pH 6 with hydrochloric acid and extracted

with chloroform. The chloroform extract was washed until neutral and concentrated and the residue was chromatographed with toluene/ethanol 99:1 over silica gel. Yield: 2.50 g of 5-(N-acetyl-N-methylsulphonylamino)-6-(2,4-difluorophenoxy)-1-indanone having a melting point of 182°C (from ethanol).

Example 5

3.53 g of 6-(2,4-difluorophenoxy)-5-methylsulphonylamino-1-indanone were dissolved in 35 ml of methanol and 10 ml of a 1N sodium hydroxide solution, and, at 5°C, 0.8 g of sodium borohydride was added in portions. After 16 hours at 20°C the whole was concentrated, 40 ml of water and 26 ml of 1N hydrochloric acid were added and the whole was filted with suction. Recrystallization from ethanol yielded 3.07 g of N-[6-(2,4-difluorophenoxy)-1-hydroxy-5-indanyl]-methanesulphonamide having a melting point of 127°C.

Example 6

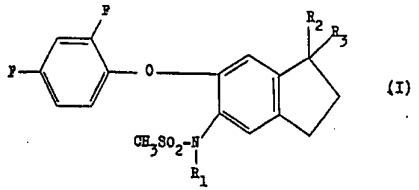
7.06 g of 6-(2,4-difluorophenoxy)-5-methylsulphonylamino-1-indanone in 100 ml of methanol and 40 ml of water were boiled with 3.40 g of sodium acetate trihydrate and 4 g of hydroxylamine hydrochloride for 3 hours. After cooling, the whole was filtered with suction and dried. Yield: 6.16 g of N-[1-hydroxyimino-6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide having a melting point of 240°C.

Example 7

3.68 g of N-[1-hydroxyimino-6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide were dissolved in 100 ml of ethanol. The solution was saturated with ammonia gas, 1 g of Raney nickel was added and hydrogenation was carried out at 90°C. Cooling, filtration, concentration, the addition of ethanolic hydrochloric acid, concentration and crystallization with ether yielded 2.99 g of N-[1-amino-6-(2,4-difluorophenoxy)-5-indanyl]-methansulphonamide hydrochloride having a melting point of 220°C.

Claims

1. An indanyl derivative of the general formula I



(I)

in which

R_1 represents a hydrogen atom, a methanesulphonyl group or an acetyl group, and

R_2 and R_3 together represent an oxo group or an oximino group or R_2 represents a hydrogen atom and R_3 represents a hydrogen atom, a hydroxyl group or an amino group.

2. A physiologically tolerable salt with an acid of a compound as claimed in claim 1 in which R_2 represents a hydrogen atom and R_3 represents an amino group.

3. A hydrochloride of a compound as claimed in claim 1 in which R_2 represents a hydrogen atom and R_3 represents an amino group.

4. N-[6-(2,4-Difluorophenoxy)-5-indanyl]-methanesulphonamide.

5. N-Acetyl-N-[6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide.

6. 6-(2,4-Difluorophenoxy)-5-methylsulphonylamino-1-indanone.

7. 5-(N-Acetyl-N-methylsulphonyl-amino)-6-(2,4-difluorophenoxy)-1-indanone.

8. N-[6-(2,4-Difluorophenoxy)-1-hydroxy-5-indanyl]-methanesulphonamide.

9. N-[1-Amino-6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide hydrochloride.

10. 6-(2,4-Difluorophenoxy)-5-bis-(methylsulphonyl)-amino-1-indanone.

11. N-[1-Hydroxylmino-6-(2,4-difluorophenoxy)-5-indanyl]-methanesulphonamide.

12. A compound selected from compounds of the general formula I given in claim 1, in which R_1, R_2 and R_3 have the meanings given in claim 1, and physiologically tolerable salts with acids of such compounds in which R_2 represents a hydrogen atom and R_3 represents an amino group, for use in a method of treatment by therapy of an inflammation.

13. The compound claimed in any one of claims 4 to 11 for use in a method of treatment by therapy of an inflammation.

14. A pharmaceutical preparation which comprises a compound selected from compounds of the

general formula I given in claim 1, in which R_1, R_2 and R_3 have the meanings given in claim 1, and physiologically tolerable salts with acids of such compounds in which R_2 represents a hydrogen atom and R_3 represents an amino group, in admixture or conjunction with a pharmaceutically suitable carrier.

15. A preparation as claimed in claim 14, containing a single compound selected from compounds of the general formula I and the physiologically tolerable salts defined in claim 14.

16. A preparation as claimed in claim 14, containing two compounds selected from compounds of the general formula I and the physiologically tolerable salts defined in claim 14.

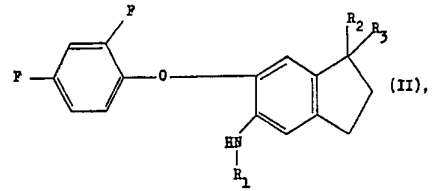
17. A pharmaceutical preparation which comprises the compound claimed in any one of claims 4 to 11, in admixture or conjunction with a pharmaceutically suitable carrier.

18. A preparation as claimed in any one of claims 14 to 17, which is in the form of a tablet, dragée, capsule, solution or inhalant.

19. A preparation as claimed in any one of claims 14 to 17, which is in a form suitable for oral administration.

20. A preparation as claimed in claim 19, which is in the form of a tablet, dragée or capsule containing 1 to 250 mg of the active substance.

21. A process for the manufacture of a compound of the general formula I given in claim 1, in which R_1, R_2 and R_3 have the meanings given in claim 1, or a physiologically tolerable salt with an acid of such a compound in which R_2 represents a hydrogen atom and R_3 represents an amino group, wherein a compound of the general formula II



(II),

in which R_1, R_2 and R_3 have the meanings given above, is condensed with methanesulphonyl chloride, and, if desired, in any resulting compoung of the general formula I in which R_2 and R_3 together represent an oxo group this oxo group is converted into an oximino group, and/or in any resulting compound of the general formula I in which R_2 and R_3 together represent an oxo or oximino group this oxo or oximino group is reduced to form a compound of the general formula I in which R_2 represents a hydrogen atom and R_3 represents a hydroxyl or amino group, respectively, and/or any resulting compound in which R_1 represents a hydrogen atom is acetylated, and/or any resulting salt is converted into the corresponding free compound, and/or any resulting compound of the general formula I in which R_2 represents a hydrogen atom and R_3 represents an amino group is converted into a physiologically tolerable salt thereof with an acid.

22. A process as claimed in claim 21, conducted substantially as described herein.

23. A process for the manufacture of a compound as claimed in claim 1 or 2, conducted substantially as described in any one of Examples 1 to 7 herein.

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